to a subject an amount of a ligand of complement receptor 3 or complement receptor 4 effective in downregulating production of interleukin-12, thereby treating [or preventing] the interleukin-12-induced inflammatory response of an autoimmune disease.

7. (Amended) A method of treating [or preventing] the interleukin-12-induced inflammatory response of an inflammatory bowel disease in a human subject, comprising administering to a subject an amount of a ligand of complement receptor 3 or complement receptor 4 effective in downregulating production of interleukin-12, thereby treating [or preventing] the interleukin-12-induced inflammatory response of an inflammatory bowel disease.

Please cancel claims 9 and 11-13, without prejudice.



REMARKS

Claims 1-13 are pending in this application. Claims 5 and 7 are amended herein for clarity to more particularly define the invention. Claims 9, 11, 12 and 13 are canceled herein without prejudice. It is believed that no new matter has been added by these amendments. Support for these amendments can be found in original Claims 5 and 7 as filed. In light of these amendments and the following remarks, applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

I. Oath

The Office Action states that the oath or declaration is defective because it does not state that the person making the oath or declaration believes the named inventor or inventors to be the original and first inventor or inventors of the subject matter which is claimed and for which a patent is sought. The Office Action also states that Page 1 of the three page oath appears to be

missing.

Applicants respectfully point out that a complete three page oath was originally filed with the present application on February 15, 1999. Applicants provide herewith a copy of the oath as originally filed which states that the person making the oath or declaration believes the named inventor or inventors to be the original and first inventor or inventors of the subject matter which is claimed and for which a patent is sought

This oath is believed to be in compliance with 37 CFR 1.67 (a). Therefore, entry of the oath and withdrawal of the statement of defective oath are respectfully requested.

I. Rejections under 35 U.S.C. § 112, first paragraph

A. Claims 5, 6, 7, 8 and 10 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of treating the interleukin-12-induced inflammatory response of inflammatory bowel disease comprising administering a ligand of complement receptor 3, allegedly does not reasonably provide enablement for preventing the interleukin-12 induced inflammatory response of inflammatory bowel disease or of any other TH-1 cell mediated autoimmune disease, comprising administering a ligand of complement receptor 3. The specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to use the claimed methods commensurate in scope with the instant claims.

Claims 5 and 7 are amended herein to recite a method of treating the interleukin-12-induced inflammatory response of an autoimmune disease in a human subject, comprising administering to a subject an amount of a ligand of complement receptor 3 or complement receptor 4 effective in downregulating production of interleukin-12, thereby treating the

interleukin-12-induced inflammatory response of an autoimmune disease and a method of treating the interleukin-12-induced inflammatory response of an inflammatory bowel disease in a human subject, comprising administering to a subject an amount of a ligand of complement receptor 3 or complement receptor 4 effective in downregulating production of interleukin-12, thereby treating the interleukin-12-induced inflammatory response of an inflammatory bowel disease, respectively.

As amended, Claims 5 and 7 do not recite methods of preventing an inflammatory response. Applicants believe that this amendment overcomes this rejection and respectfully request its withdrawal. Since Claim 6 depends from claim 5 and, Claims 8 and 10 depend from Claim 7, Applicants believe these amendments overcome the rejection of Claims 6, 8 and 10 and respectfully request its withdrawal as well.

B. Claims 7, 8 and 10 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it most nearly connected, to use the invention. The Office Action states that the specification does not enable one of skill in the art regarding the efficacy of said treatment in humans and that the efficacy of said treatment methods in the rodent models of inflammatory bowel disease disclosed in the specification may not correlate well with the efficacy of said treatment methods in humans, since it is not known the extent to which these rodent models represent true human inflammatory bowel disease (Duchmann et al. *Eur. J. Immunol.* 26: 934-938, 1996, especially page 934, column 2, lines 12-16).

Applicants respectfully direct the Examiner to MPEP 2164.02 where it is stated that if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not

correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Since the initial burden is on the examiner to give reasons for lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985).

Applicants assert that the TNBS induced colitis model is an established and art-recognized animal model of chronic inflammation developed by Morris et al. in 1989 copy included herein as (Exhibit 1). In developing this model, Morris et al. stated: "The characteristics and relatively long duration of inflammation and ulceration induced in this model afford an opportunity to study the pathophysiology of colonic inflammatory disease in a specifically controlled fashion, and to evaluate new treatments potentially applicable to inflammatory bowel disease in humans (Abstract)." Subsequent to the development of the TNBS-induced rat model by Morris et al., others have used this model to study the pathophysiology of colonic inflammatory disease and to evaluate new treatments potentially applicable to inflammatory bowel disease. As stated by Duchmann et al. (page 934 second column and page 935 first column), "Experimental colitis induced in BALB/c mice by rectal administration of the hapten reagent 2,4,6-trinitrobenzene sulfonic acid (TNBS) has recently been described by us to cause a severe transmural and chronic granulomatous inflammation associated with diarrhea, rectal prolapse and weight loss (Neurath et al. *J. Exp. Med.* 182: 1281-1290 (1995). It is further characterized by a marked infiltration of the intestine by CD4 T cells and the induction of a TH1 pattern of cytokine response. All of these clinical, histopathological, and immunological features are consistent with those found in Crohn's disease."

Based on Morris et al, Duchmann et al. and Neurath et al., it is evident that one skilled in the art would accept the TNBS mouse model as reasonably correlating to inflammatory bowel disease. Applicants have also shown that the treatment of TNBS-induced colitis with the anti-CR3 antibodies of this invention resulted in a significant clinical improvement, as measured by an increase in body weight as well as an abrogation of TH1 cytokine (IFN-γ) response.

Thus, one skilled in the art could practice the claims of the present invention with only routine experimentation using the teachings set forth in the present specification and therefore, the claimed invention is adequately enabled for treating the interleukin-12 induced inflammatory response of an inflammatory bowel disease in a human subject. Thus, it is Applicants' belief that this rejection has been overcome and Applicants respectfully request its withdrawal. If the Examiner maintains this rejection on the basis of her assertion that there is a lack of correlation between the efficacy in the established TNBS animal model and efficacy in humans, Applicants respectfully request that specific evidence demonstrating the lack of correlation be provided by the Examiner.

II. Rejection under 35 U.S.C. § 102(a)

Claims 1-2 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Marth et al. (*J. Exp. Med.* 185:1987-1995, June 2, 1997). Marth et al. teach a method of suppressing IL-12 production and its associated inflammatory response (as shown by the suppression of IFN-gamma production) in a murine model of septic shock by treatment with CR3 antibodies. Therefore, the referenced teachings allegedly anticipate the claimed invention.

Applicants respectfully point out that the authors of the Marth et al. publication are Thomas Marth and Brain L. Kelsall, both named inventors in the present application. Therefore, the Marth et al. reference is not properly cited as prior art under 35 U.S.C. § 102(a) because this

reference is not by others. Thus, Applicants believe this rejection has been overcome and respectfully request its withdrawal.

III. Rejection under 35 U.S.C. § 103(a)

Claims 1-8 and 10 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Marth et al. (*J. Exp. Med.* 185: 1987-1995, June 2, 1997) in view of Neurath et al. (*J. Exp. Med.* 182: 1281-1290, 1995) and Duchmann et al. (*Eur. J. Immunol.* 26: 934-938, 1996).

As stated above Marth et al. is not a reference "by others" and is not available as prior art against the present application. Therefore, Marth et al. should be removed as a 103(a) reference. Since there is no teaching or suggestion in Neurath et al. or in Duchmann et al. of the ability of antibodies to CR3 to ameliorate Th1 cell mediated autoimmune diseases, Applicants believe that the removal of Marth et al. overcomes the present rejection and respectfully request its withdrawal.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of the application to issue.

No additional fee is believed due; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date shown below.

Mary L. Miller — April 20, 2000
Mary L. Miller — Date